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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AFREMOVA, VERA	

ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,920	LEACH ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Clams 1-8 as amended (11/15/2007) are pending and under examination.

Claim Rejections - 35 USC § 112

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the reactive species" as second agent in a method for culturing primary hepatocytes. There is insufficient antecedent basis for this limitation in the claim. The scope of "the reactive species" is a broader than the previously recited narrow limitations "reactive oxygen" and "reactive nitrogen species" within the same claims and, thus, is considered indefinite since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. MPEP 2173.05(c). In alternative, inhibitor of "reactive species" is an anti-oxidant and, thus, the concept of using two different agents is unclear and uncertain as claimed since they are the same agents capable of the same function.

Chemical name of the presently claimed glutathione precursor compound such as "2-oxo-thiazolidine" is incorrect and/or indefinite in the lack of specific definitions in the as-filed specification because 14 different compounds incorporate "2-oxo-thiazolidine" group (see STN file Registry). Thus, it is unclear what compounds in used in the culture of hepatocytes as intended. Chemical name of the presently claimed "NG-methylarginine" is also incorrect and/or indefinite. The lack of proper chemical names adds to uncertainty about the differences between first agent and second agent particularly in view that the claimed chemicals including tocopherol

succinate, mannitol, "2-oxo-thiazolidine" and "NG-methylarginine are identified as being both agents (see claims 2 and 7 and see claims 3 and 8).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 4 as amended remain rejected under 35 U.S.C. 102(b) as being anticipated by US 5,198,432 (Fariss) in the light of evidence by ATCC catalogue and Sharma et al. (Cancer Research. 1994, 54 (2): 5848-5855).

Claims are directed to a method for culturing primary hepatocytes comprising steps of plating and culturing primary hepatocytes in the presence of two agents wherein first agent is anti-oxidant and second agent that inhibits the reactive species or increases intracellular glutathione, wherein said primary hepatocytes either maintain metabolic function or display fenestration for at least five days. Some claims are further drawn to culturing primary hepatocytes in the presence of anti-oxidant such as tocopherol succinate. Some claims are further drawn to culturing primary hepatocytes in the presence the second agent that increases intracellular glutathione or "glutathione precursor".

US 5,198,432 (Fariss) discloses a method for plating and culturing primary hepatocytes in Waymouth's medium (col.7, line 36) supplemented with antioxidant vitamin E including tocopherol succinate for 5-7 days on collagen surfaces (col. 14, lines 20-27). The Waymouth's medium contains vitamins or antioxidants that are inhibitors of "reactive species within the

broadest meaning of the claims (see ATCC catalogue page 525). The Waymouth's medium also contains folic acid that is an agent that increases intracellular glutathione as evidenced by Sharma et al. (page 5852). Thus, the method of US 5,198,432 (Fariss) for culturing primary hepatocytes comprises culturing primary hepatocytes in the presence of 2 agents within the broadest meaning of the claims. US 5,198,432 (Fariss) clearly states that hepatocytes remain viable for 5-7 days (col. 14, lines 20-27) and, thus, they are reasonably expected to maintain their metabolic activity such as metabolize xenobiotics to at least some extend. In alternative, claim limitations are drawn to hepatocyte degradation such as display of fenestration and binucleation. Thus, some cells, if not viable, are expected to display "fenestration" within the broadest meaning of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title; if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 as amended remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,198,432 (Fariss) in the light of evidence by ATCC catalogue and Sharma et al. (Cancer Research. 1994, 54 (2): 5848-5855) taken with Pourahmad et al.(IDS reference), Dilworth et al. (IDS reference) and Roberts et al. (IDS reference).

Claims are directed to a method for culturing primary hepatocytes comprising step of plating and culturing primary hepatocytes in the presence of two agents wherein first agent is anti-oxidant and second agent is a) a functional inhibitor of an enzyme that generates reactive

oxygen and reactive nitrogen species or b) an agent that directly inhibits the reactive species, or c) an agent that increases intracellular glutathione, wherein said hepatocytes either maintain metabolic function or display fenestration for at least five days. Some claims are further drawn to culturing primary hepatocytes in the presence of anti-oxidant such as tocopherol succinate or mannitol. Some claims are further drawn to culturing primary hepatocytes in the presence the second agent such as glutathione precursor or "2-oxo-thiazolidine". Some claims are further drawn to culturing primary hepatocytes in the presence of the second agent such as inhibitor of nitric oxide or "NG-methylarginine". Some claims are further drawn to culturing primary hepatocytes in the presence of "2-oxo-thiazolidine" and tocopherol succinate as first and second agents. Some claims are further drawn to culturing primary hepatocytes in the presence of "NG-methylarginine" and mannitol as first and second agents.

US 5,198,432 (Fariss) teaches protective effects of antioxidants including tocopherol succinate on lifespan of cultures of primary hepatocytes. The cited method is relied upon as explained above for culturing primary hepatocytes including the use of Waymouth's medium supplemented with antioxidants or vitamins including tocopherol succinate and with agent increasing intracellular glutathione or folic acid as evidenced by ATCC Catalogue (page 525) and by Sharma et al. (page 5852). US 5,198,432 (Fariss) also discloses culturing hepatocytes on collagen matrices for 5-7 days in the protective medium.

The culture medium in the method of US 5,198,432 does not contain 2-oxo-thiazolidine, methylarginine and mannitol as first and/or second agents. However, the references teach protective effects of the presently claimed agents including mannitol (Pourahmad et al.), 2-oxo-

thiazolidine (Dilworth et al.) and methylarginine (Roberts et al.) on cultures of hepatocytes, for example: see abstract of the cited references.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to incorporate protective agents including the presently claimed tocopherol succinate, 2-oxo-thiazolidine, methylarginine and/or mannitol in the culture of primary hepatocytes with a reasonable expectation of success in maintaining viability of hepatocytes because the presently claimed agents have been known and used for culturing and maintaining viability of hepatocytes as adequately demonstrated by the cited references combined. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 11/15/2007 have been fully considered but they are not persuasive.

With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by US 5,198,432 (Fariss) in the light of evidence by ATCC catalogue and Sharma et al. Applicants argue that US 5,198,432 (Fariss) does not teach that hepatocytes maintain their function for at least 5 days. Upon review of the reference it is not found true. US 5,198,432 (Fariss) clearly states that hepatocytes remain viable for 5-7 days (col. 14, lines 20-27) and, therefore, they are reasonably expected to maintain their metabolic activity such as metabolize generic xenobiotics to at least some extend. In alternative, the claim limitations are now also drawn to hepatocyte

degradation such as display of "fenestration" or binucleation. Thus, some cells, if not viable, are expected to display degradation or "fenestration" within the broadest meaning of the claims.

With regard to claim rejection under 35 USC § 103 applicants' main argument is that the cited references do not teach or suggest culturing hepatocytes for 5 days. This argument is not found convincing since US 5,198,432 (Fariss) clearly states that hepatocytes remain viable for 5-7 days when cultured on collagen matrices instead of suspensions in the media with protective agents including those that are presently claimed. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Moreover, the cited references teach protective effects of the presently claimed compounds when hepatocytes are exposed to toxins or to apoptosis inducing compounds and, thus, measuring protective effects within several hours would be a reasonable protocol of evaluating protective effects of beneficial compounds from lethal toxins.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1657

January 18, 2008

VERA AFREMOVA

PRIMARY EXAMINER